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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/028,410	12/19/2001	Yves Dubaquie	P1712R1-1D1	4233

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 05/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/028,410	DUBAQUIE ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *8-14* is/are withdrawn from consideration.

5)☒ Claim(s) *3-7 and 15-24* is/are allowed.

6)☒ Claim(s) *1 and 2* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-24* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/24/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment of 24 January 2005 has been entered in full. Claims 1-5 and 16 are amended. Claims 17-24 are added.

This application contains claims 8-14 drawn to an invention nonelected with traverse in the communication of 25 April 2005. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-7 and 15-24 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objection to claim 5 at pg 3 of the previous Office Action (24 August 2004) is *withdrawn* in view of the amended claim (24 January 2005).

2. The rejections to claims 3-7 and 15-16 under 35 U.S.C. 112, first paragraph (scope of enablement), as set forth at pg 3-14 of the previous Office Action (24 August 2004) are *withdrawn* in view of the amended claims and Applicant's persuasive arguments (24 January 2005). Please see section on 35 U.S.C. § 112, first paragraph below.

3. The rejection of claim 5 under 35 U.S.C. § 112, first paragraph (written description) as set forth at pg 14-16 of the previous Office Action (24 August 2004) is *withdrawn* in view of the amended claim and Applicant's persuasive argument (24 January 2005).

4. The supplemental information disclosure statement filed on 24 January 2005 has been considered.

Claim Rejections - 35 USC § 112, first paragraph

5. Claims 1-2 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1 is directed to a method for increasing active IGF-I levels in a mammal comprising administering to the mammal an effective amount of an Insulin-like Growth Factor-I (IGF-I) variant wherein the amino acid residue at position 16, 25, or 49 or the amino acid residues at positions 3 and 49 of native-sequence human IGF-I are replaced with an alanine, a glycine, or a serine residue. Claim 2 recites wherein the mammal has increased Insulin-like Growth Factor Binding Protein-I (IGFBP-I) levels relative to such levels in a normal mammal.

Applicant's arguments filed 24 January 2005, as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) At page 9 of the Response of 24 January 2005, Applicant asserts that undue experimentation would not be required to identify individuals with reduced IGF-I levels. Applicant argues that determination of levels of active IGF-I, IGFBP-1, and IGFBP-3 can be done through standard clinical means, such as ELISA, RIA, or bioassay. Applicant cites page 22, lines 11-30, which described methods for measuring the level of active IGF-I levels. Applicant also indicates that Example 3 of the instant specification, Example 4 of WO 98/45427, and U.S. Patent 5,565,428 describe methods of measuring IGF-I, IGFBP-1, and IGFBP-3. Additionally, Applicant contends U.S. Patent Nos. 5,565,428 and 5,741,776 teach various methods of administration and dosages of wild-type IGF-I to treat human patients for a broad

range of diseases. Applicant states that accordingly, an IGF-I variant of the instant invention could be administered by these methods.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, undue experimentation would be required by one skilled in the art to identify a patient population in need of increased active IGF-I levels. The instant claims fail to recite limitations as to specific mammals that are in need of increased active IGF-I levels. Example 3 of the instant specification only teaches the administration of IGF-I to patients with diabetes and measurement of the concentrations of IGF-I, IGF-II, and IGFBP-3 (pg 42). These experiments are not adequate guidance, but are merely an invitation for the artisan to use the current invention as a starting point for further experimentation. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed".

The specification of the instant application discloses that disease states characterized by low IGF-bioactivity may include hyperglycemic disorders, renal disorders, congestive heart failure, hepatic failure, poor nutrition, Turner's syndrome, Downs' Syndrome, a wasting syndrome involving a decrease in protein synthesis such as AIDS wasting, and catabolic states characterized by increased IGFBP levels (such as a critical illness, a disorder involving a decrease in nitrogen balance, and protein catabolism caused by glucocorticoid excess) (pg 11, lines 27-35 through pg 12, lines 1-5). Additionally, WO 98/45427 (cited in Example 3 (pg 42-43) of the instant application) teaches that diseases associated with a lack of active IGF-I in the bloodstream include diabetes, obesity, anabolic disorders, immunologic disorders, cardiac disorders, and renal disorders (pg 44, lines 9-10). The Examiner has broadly interpreted claims

1-2 as encompassing all possible patient populations, including patients with such conditions as indicated above. However, the numerous disorders, diseases, and conditions encompassed by claims have different pathophysiologies and one skilled in the art would not be able to predict from the instant specification that an IGF-I variant recited in the claims would be able to treat all possible patient populations that exhibit a need for increasing active IGF-I levels. For example, as discussed in the previous Office Action of 24 August 2004, Down's syndrome is the most frequent form of mental retardation caused by a triplicate state (trisomy) of all or a critical portion of chromosome 21. A few of the major characteristics of Down's syndrome include mental retardation, ocular anomalies, skeletal anomalies, congenital defects (see Appendix A in the Office Action of 18 July 2003; http://www.emedicine.com/derm/topic687.htm#section~clinical). Congestive heart failure is a condition in which the heart can't pump enough blood to the body's organs. Congestive heart failure is an imbalance in starling forces or an imbalance in the degree of end-diastolic fiber stretch proportional to the systolic mechanical work expended in a contraction (see Appendix B in the Office Action of 18 July 2003; http://www.emedicine.com/emerg/topic108.htm). Renal hypertension is high blood pressure caused by the narrowing of the arteries that carry blood to the kidneys. A reduced blood flow to the kidneys leads to excessive release of the hormone, renin, which increases blood pressure (see Appendix C attached to the Office Action of 24 August 2004; http://www.nlm.nih.gov/medlineplus/ency/article/000204.htm).

Furthermore, the state of the art at the time the invention was made teaches that activated IGF-I and its receptor display mitogenic, transforming, and anti-apoptotic properties and that high circulating levels of IGF-I are positively associated with risk of prostate cancer and breast

cancer among premenopausal women (Wolk et al. J Natl Cancer Instit 90(12): 911-915, 1998; Chan et al. Science 279 : 563-566, 1998 ; Hankison et al. Lancet 351 : 1393-1396, 1998). Therefore, undue experimentation would be required by the skilled artisan to identify a patient population in need of increased active IGF-I levels. The present invention is also unpredictable and complex wherein one skilled in the art may not necessarily increase active IGF-I levels in a mammal because, as the specification of the instant application discloses (pg 42, lines 31-33; pg 43, lines 11-13), concentrations of IGF-I in the blood reach a plateau.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to increase active IGF-I levels in all possible patients with any condition, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, the unpredictability of the effects of increasing active IGF-I levels by administering an IGF-I variant, and the breadth of the claims which fail to recite limitations as to the patient population in need of increased IGF-I levels and the condition to be treated, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

Claims 3-7 and 15-24 are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

BEB
Art Unit 1647
13 May 2005

ELIZABETH KEMMERER
PRIMARY EXAMINER